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Double-blind comparison of two regimens in the treatment of nongonococcal urethritis*

Seven-day *vs* 21-day courses of triple tetracycline (Deteclo)

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SUMMARY In a double-blind comparison of two regimens of triple tetracycline (Deteclo, Lederle) in the treatment of nongonococcal urethritis, 62 (88·6%) of 70 patients treated with one tablet twice daily for 21 days and seen four weeks after starting therapy had satisfactory results. This was significantly better than the findings among the 73 patients treated with one tablet twice daily for seven days and followed for four weeks, among whom only 47 (64·4%) had satisfactory results. Results were also better for the group treated with the 21-day regimen at three months after the start of treatment. When analysed individually at four and 12 weeks, urethral discharge, urethral Gram-stained smears, and first-glass urine test all gave similar results, which were markedly better than those before treatment. It appears that the longer course of treatment is indicated where any regular partner may not be treated. Slightly fewer patients had satisfactory results among those who admitted consuming alcohol than among those who did not. Chlamydiae-negative patients, treated for seven days, had fewer clinically satisfactory results than other sub-groups.

Introduction

The tetracycline group of drugs appears to be among the most effective agents for treating nongonococcal urethritis (NGU) (Morton 1975; King and Nicol, 1975). Although many tetracycline preparations and dosages have been described few comparative trials have been carried out.

In this report, we describe the results of a double-blind trial of the triple tetracycline, Deteclo (Lederle), one tablet given every 12 hours for seven days, compared with one tablet given every 12 hours for 21 days.

Methods

PATIENTS

The aim was to study an unselected group of men presenting consecutively with nongonococcal urethritis (NGU). As NGU varies in clinical severity we decided to include only men with a visible discharge containing at least 10 leucocytes per microscopic field in at least 20 fields examined with a × 100 objective and × 8 eyepieces using only one microscope. Patients with a history of hypersensitivity to tetracyclines were excluded as were men taking antacids, milk, or oral iron, patients with a previous history of hepatitis, and patients who were unable to attend for three months' observation after treatment.

INVESTIGATION

Before treatment was started, urethral secretions were collected for Gram staining and microscopy for leucocytes, organisms, and fungal elements. A culture was taken for *Neisseria gonorrhoeae* and a wet preparation was examined microscopically for *Trichomonas vaginalis*. In addition, a urethral swab was taken for culture for *Chlamydia trachomatis*. Urine was examined by the two-glass test. These investigations have been described in greater detail by Alani *et al.* (1977).

DRUG ADMINISTRATION

The study was double-blind, with patients randomly allocated to one of two treatment groups.

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21-day regimen
Patients in this group were given one Deteclo tablet twice daily for 21 days.

Seven-day regimen
Patients in this group were given one Deteclo tablet twice daily for seven days, followed by one identical placebo tablet twice daily for 14 days.

Patients were instructed not to take the tablets with milk.

OBSERVATION AFTER TREATMENT

Patients were asked to attend one, four, eight, and 12 weeks after starting treatment and to hold their urine for at least four hours before attending. At each visit they were examined for the presence of visible urethral discharge, and material for Gram staining and for microscopy for leucocytes, together with a culture for gonococci, were collected after gentle urethral massage. A urethral culture for *C. trachomatis* was collected and the urine was examined by the two-glass test.

All clinical observations and results of laboratory investigations were entered on a special proforma; only the data recorded before treatment and at four and 12 weeks after the beginning of therapy are reported here.

Retreatment (either because of reinfection or treatment failure) was indicated if:

(1) Four weeks after starting treatment, a urethral discharge, containing at least 10 leucocytes per microscopic field on Gram stain as already defined, was present;

(2) At later follow up, urethral discharge containing leucocytes in the Gram stain as defined or haze, specks, or threads in the first urine glass containing leucocytes in the centrifuged deposit in the numbers already defined were present.

Patients without a discharge and with clear first urine were regarded as having a satisfactory outcome.

The effect of treating regular female partners was assessed; regular partners were those with whom the patient had had contact more than twice in the preceding three months (Alani *et al.* (1977).

During the period of the trial, approximately 90% of Gram staining and microscopy was performed by one male nurse, and all slides were kept and checked by one doctor; 90% of urinoscopy was also performed by one observer.

Statistical comparisons were made using Yates's χ^2 test and Fisher's Exact test.

Results

Of a total of 200 patients who started treatment, 57 were excluded for various reasons such as failure to attend for follow up and finding gonococci on culture. Thus, of the remaining 143 patients, 70 were treated with the 21-day regimen and 73 with the seven-day regimen of Deteclo, all of whom completed four weeks' follow up.

After treatment and follow up and before the treatment code was broken, a general appraisal of outcome was made according to the stated criteria and cases were classified as having a satisfactory outcome or a recurrence (treatment failure or reinfection).

Once the code had been broken, statistical analysis showed that the patients in the two groups resembled each other in age distribution, country of origin, marital state, history of previous urethritis, chlamydial culture results, follow-up pattern, and time urine had been held before initial examination and investigation.

By four weeks after the start of treatment, a satisfactory overall response was found in 89% of cases treated for 21 days and in 64% of cases treated for seven days (Table 1). By twelve weeks after the start of treatment findings were satisfactory in 74% of cases treated for 21 days and in 61% of those treated for seven days (Table 1). The difference in findings at four weeks is statistically significant.

The urethral discharge, urethral smear, and urinary findings on which clinical assessment of recurrence was based are shown in Table 2. A comparison between the findings at four weeks and at 12 weeks with the pre-treatment findings was noteworthy ($P<0.001$ in all cases). The comparison of findings between the two regimens was less marked ($P<0.01$ at four weeks in all cases; no significant differences at 12 weeks) as would be expected from the findings in Table 1. Comparison between the numbers of normal and abnormal findings in each parameter with the figures for each of the other two parameters at four and 12 weeks showed no differences.

The relationship of sexual intercourse during treatment or follow up or both to clinical outcome is shown in Table 3. Although the numbers with recurrence after 12 weeks were small, approximately the same proportion of patients admitted sexual

Table 1 *Overall results of treatment*

Treatment regimen with Deteclo	*No. with clinically satisfactory results (out of no. followed up) at*			
	Four weeks		*12 weeks*	
	No.	*%*	*No.*	*%*
21-day	62/70*	88·6	38/51†	75·5
7-day	47/73*	64·3	32/52†	61·5

*$\chi^2_1 = 10.25$, $P<0.01$
†$\chi^2_1 = 1.44$, $P<0.25$

Table 2 *Detailed findings before and after treatment*

	% in each drug-treatment group					
	With urethral discharge		Abnormal Gram-stain		Abnormal first-urine findings	
Examination	7-day	21-day	7-day	21-day	7-day	21-day
Before treatment	94	96	97	100	87	89
At four weeks	29	14	33	11	48	20
At 12 weeks	0	7	4	6	3	14

Table 3 *Sexual intercourse during follow up*

		No. admitting intercourse during			
		Weeks 1-4		Weeks 5-12	
Clinical outcome	Treatment group	No	Yes	No	Yes
Satisfactory	21 days	34	4	11	22
	7 days	26	5	4	22
Recurrence	21 days	5	1	3	2
	7 days	10	2	2	5

No significant differences

intercourse as among those with a satisfactory outcome.

The effect on results at four weeks of treating regular female partners, who attended this department, was examined and the findings are shown in Table 4. Although few partners attended, the findings suggested that, in the group treated with the 21-day regimen, treatment of regular partners had little effect on the patients' failure rate. Among those treated for only seven days, however, the recurrence rate was significantly higher when the partner was not treated.

The effect of alcohol consumption during the four weeks after starting treatment is shown in Table 5. Alcohol was associated with a slightly higher recurrence rate in both groups.

In Table 6, the outcome at 12 weeks is compared with any past history of urethritis (admitted in the history or recorded in the clinical documents); with both regimens a satisfactory outcome was strongly associated with no previous urethritis and recurrence with a past history of urethritis.

Table 4 *Effect of treating regular female partners on findings four weeks after start of treatment*

	Treatment group	Satisfactory outcome	Recurrence	
			No.	%
Partner treated	21 days	14	4	22·2
	7 days	14	4	22·2
Partner not treated	21 days	20	4	16·7
	7 days	7	9	56·2

In comparison of results of two regimens when partner not treated $\chi^2_1 = 5{\cdot}17$, $P<0{\cdot}05$

Table 5 *Relation between admitted alcohol consumption and clinical outcome at four weeks*

	Treatment group	Satisfactory outcome	Recurrence	
			No.	%
Alcohol	21 days	30	5	14·3
	7 days	27	12	30·8
No alcohol	21 days	26	3	10·3
	7 days	17	6	26·1

No significant differences

Table 6 *Relation of outcome at 12 weeks to past history of urethritis*

History of urethritis	Treatment group	Satisfactory outcome	Recurrence
Positive	21 days*	10	9
Negative		28	4
Total		38	13
Positive	7 days†	9	12
Negative		23	8
Total		32	20

* $\chi^2_1 = 5{\cdot}91$, $P<0{\cdot}025$
† $\chi^2_1 = 3{\cdot}95$, $P<0{\cdot}05$

CHLAMYDIAL CULTURE RESULTS

Positive *C. trachomatis* culture results were obtained before treatment from 16 (23%) patients treated for 21 days and from 12 (16%) treated for seven days (Table 7). Only one patient had a positive culture result after therapy and it is not clear why (Table 7).

The clinical response four weeks after starting therapy in relation to the *C. trachomatis* findings

Table 7 *Chlamydial culture results before and after treatment*

	Positive culture results (in relation to treatment)		
	Before	*Four weeks after*	*12 weeks after*
Treatment group	*No. %*	*No. %*	
21 days	16 22·9	0	0
7 days	12 16·4	1 2·5	0

before the start is shown in Table 8. No relation was evident between outcome and chlamydial culture result in the group treated for 21 days; in the group treated for seven days a higher recurrence rate occurred in the culture-negative patients than in the culture-positive patients.

Table 8 *Clinical response in relation to chlamydial culture results before treatment*

Treatment group	*Outcome at four weeks*	*Chlamydial culture result before treatment* +	−	*Probability*
21 days	satisfactory	5	21	0·661
	recurrence	2	9	
7 days	satisfactory	8	17	0·067
	recurrence	1	14	

+ positive − negative

Discussion

The results indicate that a better cure rate can be expected after 21 days of treatment than after seven days of treatment. The results with the 21-day regimen, however, were not as good as the 20-day regimen with oxytetracycline reported by John (1971); the seven-day regimen gave similar results to the five-day regimen with oxytetracycline described by John (1971). Although he (John, 1971) was working in this department, his methods and criteria were different.

Unfortunately, like so many other studies of the treatment of NGU, there was a high default rate but this was similar in the two groups; this may be one reason for the lack of significant difference between the results from the two treatment groups at 12 weeks. Results of studies in different departments cannot be closely compared. Our follow-up rate was worse than in some studies (Bhattacharyya and Morton, 1975) but better than others (Willcox, 1968).

The improvement in urethral discharge, urethral smear, and first urine findings appeared sooner in patients treated for 21 days than in those treated for seven days (Table 2). By 12 weeks, however, the response was similar in the two groups. Morton and Read (1957) and Fowler (1970) observed that recurrence was more common in patients treated with tetracycline than in those given a placebo. It is interesting to speculate on these differences. Perhaps the short course fails to eliminate causative micro-organisms or their antigens and allows better development of natural immunity which produces improvement. Critical analysis of these findings supported the preliminary overall general assessment. We had wondered if comparison of each parameter with the others might show differences indicating one which was more or less sensitive, but all appeared to give similar findings.

Opinions vary concerning the need for prolonged follow up. Our findings support the need for this even after 21 days of treatment.

Patients are usually advised to avoid intercourse during antimicrobial treatment and for a period afterwards (King and Nicol, 1975). In our study, recurrence and further intercourse were not related, (Table 3) although this may have been because we did not differentiate between treatment failure and reinfection. This contrasts with the report by Perera (1975). Despite the present findings, and until more equally critical studies have been undertaken, it appears wise to continue to advise patients to abstain from sexual intercourse during, and for a while after, treatment.

It is in doubt whether or not partners of men with NGU should be treated (Bhattacharyya and Morton, 1973; Evans, 1977). Although the numbers were small, our findings (Table 4) showed that among those whose partners were not treated patients given the seven-day regimen had a significantly higher recurrence rate than patients given the 21-day regimen. Thus, when there is doubt if a partner can be traced and treated a 21-day course of treatment should be prescribed.

It is also common practice to advise avoidance of alcohol (King and Nicol, 1975); Perera (1975) found a link between recurrence and alcohol consumption. The higher recurrence rate associated with alcohol consumption in our study (Table 5) supports this view, and although differences were not significant it appears wise to advise patients to avoid alcohol.

The correlation between recurrence and a past history of urethritis (Table 6) is in agreement with the findings of Morton and Read (1957) but contrasts with those of Evans (1977, 1978). Evans (1977, 1978), however, excluded patients treated for NGU during the year before his study.

It is interesting that the recurrence rate among the chlamydiae-negative cases treated for seven days was higher than in the other group (Table 7). This is in keeping with the findings reported by Handsfield *et al.* (1976) from Seattle, USA.

The main conclusions to be drawn from this study are that Deteclo, one tablet given twice daily for 21 days, gives better results than one tablet given twice daily for seven days. The longer course should be given when any regular partner may not be traced and treated.

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References

Alani, M. D., Darougar, S., Burns, D. C. M., Thin, R. N., and Dunn, H. (1977). Isolation of *Chlamydia trachomatis* from the male urethra, *British Journal of Venereal Diseases,* **53,** 88-92.

Bhattacharyya, M. N. and Morton, R. S. (1973). Long-term triple tetracycline (Deteclo) treatment of non-specific urethritis, *British Journal of Venereal Diseases,* **49,** 521-523.

Evans, B. A. (1977). The role of tetracyclines in the treatment of non-specific urethritis, *British Journal of Venereal Diseases,* **53,** 40-43.

Evans, B. (1978). Treatment and progress of non-specific genital infection, *British Journal of Venereal Diseases,* **54,** 107-111.

Fowler, W. (1970). Studies in nongonococcal urethritis therapy; the long-term value of tetracycline, *British Journal of Venereal Diseases,* **46,** 464-468.

Handsfield, H. H., Alexander, E. R., Wang, S. P., Pedersen, A. H. B., and Holmes, K. K. (1976). Differences in the therapeutic response of chlamydia-positive and chlamydia-negative forms of nongonococcal urethritis, *Journal of the American Venereal Disease Association,* **2,** 5-9.

John, J. (1971). Efficacy of prolonged regimens of oxytetracycline in the treatment of nongonococcal urethritis, *British Journal of Venereal Diseases,* **47,** 266-267.

King, A., and Nicol, C. (1975). *Venereal Diseases,* third edition, p. 263. Bailliere Tindall: London.

Morton, R. S., and Read, L. (1957). Nongonococcal urethritis, *British Journal of Venereal Diseases,* **33,** 223-226.

Morton, R. S. (1975). *Recent Advances in Sexually Transmitted Diseases.* Edited by R. S. Morton and J. R. W. Harris, first edition, p. 296. Churchill Livingstone: Edinburgh and London.

Perera, P. (1975). Evaluation of a sustained release oral tetracycline in non-specific urethritis. *British Journal of Venereal Diseases,* **51,** 333-335.

Willcox, R. R. (1968). Erythromycin in the treatment of non-gonococcal urethritis. *British Journal of Venereal Diseases,* **44,** 157-159.